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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/489,079	01/21/2000	Patricia A. Billing-Medel	6451.US.P1	5338

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 08/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/489,079	BILLING-MEDEL ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52-61,69 and 77-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-61,69 and 77-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 July 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5-27-2005 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Interview Summary

3. It is noted that the examiner contacted Mimi Goller on 7-27-05 to discuss the potential allowance of the instant claims based upon the significant homology shared between BS322 (SEQ ID NO: 24-25) and the NY-BR-1 polypeptide disclosed by Jager et al. (2001, Cancer Research, Vol. 61, pages 2055-2061). However, upon further consideration of the evidence set forth in the specification as originally filed, and the post-filing date of the Jaeger et al. reference, as per MPEP § Applicants cannot rely upon the disclosure of a post-filing reference to teach the skilled artisan how use the instantly claimed invention.

Response to Amendment

4. The amendment to the claims filed on 5/27/05 does not comply with the requirements of 37 CFR 1.121(c) because claim 80, line 5, recites the deletion of the term "is" however the status of claim 80 indicates that it was (Previously Presented). Amendments to the claims filed on or after July 30, 2003 must comply with 37 CFR 1.121(c).

Response to Arguments

Claim Rejections - 35 USC § 112

5. Claims 57-58, 61, 77-79 and 81 remain rejected, and claims 52-56, 59-60, 69, and 80 are rejected under 35 U.S.C § 112, 1st paragraph as failing to comply with the written description requirement for the reasons of record set forth in the prior Office action of 3/24/2004.

6. Applicant's arguments filed 5-27-05 with respect to the rejection of record under 35 U.S.C §112 1st have been fully considered but they are not persuasive. Applicant traverses the instant rejection on the same grounds as those set forth in the previous Response, on page 7 of the response, in the 1st paragraph it is stated that "[T]he arguments made in the previous Response are incorporated herein." Applicants noted that the claims at issue no longer recite the "50% identity" language, and based upon this Applicants assert that the claims are not drawn to a broad genus of polypeptides as purported by the Examiner, and therefore requested withdrawal of the rejection. The examiner notes that the prior rejection improperly referred to "50% identity language" that is no longer recited in the claims.

7. However, contrary to Applicant's assertions, it remains that the instant claims are still considered to read on a broad genus of polypeptides. Claim 52 recites "[A] purified polypeptide ***having*** an amino acid sequence selected from the group consisting of: SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, and SEQ ID NO: 28." It is noted that the term "having" is interpreted broadly, therefore the scope of the instant claims encompasses polypeptides of undefined length which comprise one of the amino acid sequences of SEQ ID NO: 24-28, wherein these amino acid sequence encompasses from 38 to 398 amino acids. Moreover, claims 57-59, 61, 69, 77-79 recite an immunogenic polypeptide comprising at least

one BS322 epitope derived from an amino acid sequence selected from the group consisting of SEQ ID NO: 24-28. On page 20 of the specification, Applicants define "epitope" as "[a]n antigenic determinant of a polypeptide or protein. Conceivably, an epitope can comprise three amino acids in a spatial conformation that is unique to the epitope. Generally, an epitope consists of at least five such amino acids and more usually, it consists of at least eight to ten amino acids." Conformational epitopes are defined as "an epitope that is comprised of a specific juxtaposition of amino acids in an immunologically recognizable structure, such amino acids being present on the same polypeptide in a contiguous or non-contiguous order or present on different polypeptides." Moreover, Applicants state "[A] polypeptide is "immunologically reactive" with an antibody when it binds to an antibody due to antibody recognition of a specific epitope contained within the polypeptide."

Applicant's own specification suggests that amino acid sequence of SEQ ID NO:s 26-28 are not full-length proteins, for example, on page 11, lines 1-14, it states that the clone according to SEQ ID NO: 8 represents a full length sequence, and that SEQ ID NO: 1-8 are overlapping clones. Therefore, from these overlapping clones, applicants designed a "consensus" sequence, SEQ ID NO: 9. Moreover, at page 49, lines 5-20, Applicants stated that the polynucleotides of SEQ ID NO: 1-9 may "contain an entire open reading frame with or without associated regulatory sequences for a particular gene, or they may encode only a portion of the gene of interest." From this passage of the specification, it is clear that Applicants were not aware that they were in possession of the full-length nucleotide sequence of BS322. This statement clearly suggested that further experimentation would be required in order to confirm that they were in possession of the full-length gene sequence. In the response filed 11/06/2003 (see page 3),

Applicants made several statements suggesting that the BS322 consensus polynucleotide (SEQ ID NO: 9, and encoding SEQ ID NO: 25), represents a splice variant of NY-BR-1. These statements on the record by Applicants clearly suggest that Applicants were not in possession of a full length sequence at the time of the instant invention, and that by further experimentation the full length clone, NY-BR-1 was isolated.

Therefore the scope of the reads on full-length polypeptides comprising essentially fragments of 38 amino acids in length. The claims also encompass BS322 polypeptides that contains at least one BS322 epitope, wherein an epitope may comprise only three amino acids, or more preferably 8-10 amino acids "derived from" an amino acid sequence selected from the group consisting of SEQ ID NO: 24-28. Since Applicants do not set forth any guidance regarding how to determine which amino acids of SEQ ID NO: 24-28 function as an immunologically reactive BS322 epitope, it is apparent that the skilled artisan would have to resort to further trial and error experimentation to identify the full scope of BS322 polypeptides encompassed by the instant claims.

Claim Rejections - 35 USC § 101

8. The rejection of claims 52-61, 69 and 77-81 under 35 U.S.C § 101 and §112 (lack of enablement) is maintained for the grounds of rejection set forth in the prior Office action, mailed 3/24/2004, and those reasons set forth below.

9. The previous basis for the instant rejection was on the grounds that the asserted utility of the claimed polypeptides lacked credibility. The examiner would like to clarify on the record, that Applicant's asserted utility for the polypeptides of SEQ ID NO: 24-28, at the time of filing, additionally was neither substantial, nor specific. In particular, the specification as filed (page 1,

lines 10-17) states that "[T]his invention relates generally to detecting diseases of the breast....The polynucleotide and polypeptide sequences are useful for detecting, diagnosis, staging, monitoring, prognosticating, in vivo imaging, preventing or treating, or determining the predisposition to diseases or conditions of the breast, such as breast cancer." However, the asserted the asserted utilities for the polypeptides according to SEQ ID NO: 24-28 is neither specific, nor substantial.

First, it is noted that the asserted use of the polypeptides according to SEQ ID NO: 24-28 for diagnostic or therapeutic purposes, is neither substantial nor specific due to being generic in nature and applicable to a myriad of such compounds. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the polypeptides according to the present invention, such that another non-asserted utility would be well established for the compound.

Moreover, since applicants have not provided any direct evidence demonstrating a direct correlation between the over-expression of the nucleic acid encoding the polypeptides of the present invention in breast tumor tissue, and the level of polypeptide present in the diseased breast tissue. One of skill in the art would not accept on its face that the mRNA expression level in a cell is immediately correlative or even representative of the level of polypeptide produced in said cell. See Anderson et al. (Electrophoresis 1997, Vol. 18, pages 533-537), which addresses the extent to which mRNA abundances are predictive of protein abundances. In regards to the human liver, Anderson et al. teach "[A] correlation coefficient of 0.48 was obtained between the mRNA and protein abundances determined.....suggesting that post-transcriptional regulation of gene expression is a frequent phenomenon in higher organism." (See Abstract). In one specific

example, Anderson et al. show in the comparison of the β and γ actins "persuasive evidence of post-transcriptional regulation," wherein the two proteins are essentially identical in function but have "mRNA-to-protein ratios differing by more than a factor of two between the two genes (page 536, bridging paragraph)." Additionally, Anderson et al. concludes: "[H]ence it appears likely that of the total protein abundances is significantly different from that of mRNAs,...and that techniques able to detect down to a specified percent abundance threshold would reveal more proteins at a given threshold than mRNAs." (Discussion, page 537, last paragraph)

Based upon the observations made by Anderson et al., the prior art at does not provide adequate support for Applicant's direct correlation between the abundance of the mRNA transcript in breast-tumor tissue and the relative abundance of the polypeptide expression in this same tissue. Therefore, Applicant's asserted utility of the polypeptides according to SEQ ID NO: 24-28 for diagnosis or monitoring of breast cancer is neither specific, nor substantial.

Response to Arguments

10. Applicant's arguments filed 5/27/05 have been fully considered but they are not persuasive.

Applicants traversed the instant rejection on the same grounds as set forth in the previous Responses filed 6/24/04 and 11/06/03, see page 8, paragraphs 3-7 of the Response filed 5/27/05. It is noted that Applicant's arguments with respect to the Responses of 6/24/04 and 11/06/03 were previously addressed in the Office Actions mailed 9/15/04 and 3/24/04, respectively.

Moreover, on page 9 of the 5/27/05 Response, Applicants further argued that it appears that the examiner has a difficult time accepting the difference of over 1,000 nucleotides between BS322 and NY-BR-1. In response, Applicants provided an excerpt from Voet et al. (1999), to

provide support their assertion that "[i]t is common to have a very large number of nucleotides in the genetic code that are introns and are not present in the mature sequence." The examiner does not disagree with this assertion, however it is noted that the specification as originally filed provides no evidence that the consensus sequence of SEQ ID NO: 9, or the "full-length" sequence of SEQ ID NO: 8, represent a splice variant of a larger sequence. The original specification did not provide a Northern Blot analysis using SEQ ID NO: 8 or 9 as a probe, wherein mRNA structures of at least 1,000 nucleotides in length were revealed by hybridization. As set forth in the prior Office action and as pointed out by Applicant in the instant communication, the NY-BR-1 splice variants of Jaeger et al. are highly similar, differing by only 111 bp. Applicant has argued previously that, based on nucleotide similarity, BS322 is a splice variant of NY-BR-1 (communication filed 11/06/2003, pg 3). However, it is noted herein that the nucleotide sequence of BS322 is disclosed as 2683 base pairs in length while the nucleotide sequence of NY-BR-1 is disclosed as 4463 base pairs in length. Given the large length differences between these two molecules as compared to the differences observed between NY-BR-1 and the known NY-BR-1 splice variants of Jaeger et al., sound scientific reasoning dictates that specific and particular evidence of the alternative splicing and maturation of a splice variant that is the considerably shorter BS322 nucleotide sequence (as compared to NY-BR-1) would be required to demonstrate that BS322 was indeed a splice variant of NY-BR-1.

Furthermore, the Jaeger et al. used RT-PCR to analyze NY-BR-1 and its splice variant NY-BR-1.1 (see page 2058), the examiner has compared the sequence of SEQ ID NO: 8 with the sequence of NY-BR-1.1, these sequences are about 65% identical. If BS322 represents a splice

variant of NY-BR-1, it is unclear why the experiments of Jaeger et al. did not reveal another mRNA transcript other than NY-BR-1.1 during their analyses.

Moreover, because of the over abundance of the BS322 polynucleotide of SEQ ID NO: 9 and fragments thereof, SEQ ID NO: 1-8, in breast tissues in comparison to non-breast libraries as set forth on page 63 of the specification as originally filed, and similarity with the NY-BR-1 gene, the examiner agrees that there is utility for the polynucleotides of the present invention. However, at the time of the instant invention, Applicants did not provide sufficient evidence of utility for the claimed polypeptides, for this reason the instant rejection has been maintained throughout the lengthy prosecution of the instant application. To date Applicants have not provided any evidence (for example in the form of a Declaration) of a correlation between the overexpression of the BS322 polynucleotide of SEQ ID NO: 9, and the overexpression of SEQ ID NO: 24-28 in breast tissue, such that the prosecution record clearly demonstrates that SEQ ID NO: 24-28 function as breast cancer antigens, and therefore useful for diagnostic and/or therapeutic purposes as suggested by Applicant on page 1, lines 10-17 of the instant application. There was no evidence in the specification as filed, or provided in the form of a Declaration, that would indicate that the claimed polypeptides according to SEQ ID NO: 24-28 were over expressed in breast cancer tissue in comparison to normal tissue. Furthermore, it is noted that page 63, lines 20-32, do not indicate that the libraries were from diseased breast tissue, in comparison to non-diseased breast or non-diseased non-breast tissue. However, the similarity between SEQ ID NO: 9 and the nucleotide sequence encoding NY-BR-1 suggests that SEQ ID NO: 9 could be used to assay for the over expression of mRNA encoding NY-BR-1 in a test sample. The only real asserted utility for the claimed polypeptides is for the production or

identification of BS322 specific antibodies. However, it is clear that the amino acid sequences of SEQ ID NO: 26-28 were derived from SEQ ID NO: 24-25 (see page 76, lines 9-12), therefore it is clear that they do not exist under normal cellular conditions. Moreover, Applicants have not provided sufficient evidence to demonstrate that the polypeptides of SEQ ID NO: 26-28 function as immunologically reactive BS322 epitopes, therefore use of antibodies that bind SEQ ID NO: 26-28 is uncertain.

Jaeger et al. (WO 200147959 A2) at page 24, describes a screen of multiple peptide fragments of NY-BR-1, however only 3 peptides were identified as immunoreactive peptides that function to stimulate cytotoxic T-cells, having the following sequences: LLSHGAVIEV (102-111 of NY-BR-1), SLSKILDTV (amino acids 904-912 of NY-BR-1), and SLDQKLFQL (amino acids 1262-1270 of NY-BR-1). It noted that only SEQ ID NO: 25 comprise the SLDQKLFQL sequence, however at the time of filing of the instant application, apart from further experimentation, the skilled artisan would not have known that the SLDQKLFQL fragment of SEQ ID NO: 25 would function as an immunoreactive peptide. Moreover, it is noted that SEQ ID NO: 24, and 26-28 do not comprise any of the other immunoreactive peptides described by Jaeger et al.

Due to the unpredictability associated with correlating mRNA abundance with the corresponding polypeptide or protein abundance, as taught by Anderson et al., the ordinary skilled artisan would not accept on its face that overexpression of mRNA in breast tissue would necessarily correlate with high polypeptide expression. Although, Jaeger et al. teach the potential use of specific peptide fragments of NY-BR-1 as immunoreactive peptides, there is no guidance in the instant specification, or known in the art, as how to use the claimed polypeptides, in

particular peptides 26-28, throughout the full scope of the claimed invention, apart from undue experimentation. As per MPEP § 2164.05(a) [R-2] a specification must be enabling as of the Filing Date. Applicants cannot rely upon the teachings of a post-filing reference to provide evidence that Applicants have taught how to use the instantly claimed invention.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571)272-0731. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Epps-Ford, Ph.D.
Patent Examiner
Art Unit 1633

JLE